REMARKS

The Specification has been amended to update the status of the priority applications. The claims have been amended, and other claims have been canceled, in order to expedite prosecution.

Rejection of Claims under 35 U.S.C. §112, first paragraph

The Examiner rejected Claims 35-64, stating that the claims were not enabled by the specification. Applicants respectfully disagree.

As amended, the claims are drawn to a method of treating a human patient with Pompe's disease by intravenously administering biweekly to the patient a therapeutically effective dose of human acid alpha glucosidase, whereby the concentration of accumulated glycogen is reduced and/or further accumulation of glycogen is arrested. As described in the Specification, a therapeutically effective dose for treatment of a lysosomal enzyme deficiency disease is a dose that is sufficient to reduce the concentration of accumulated metabolite and/or prevent or arrest further accumulation of metabolite (see p. 18, line 29, through p. 19, line 2). In the case of Pompe's disease, it is glycogen that accumulates. The Specification describes in detail a set of experiments using a knock-out mouse model generated by targeted disruption of the murine alpha-glucosidase gene (see Example 4, pp. 27 *et seq.*). This model is known to those of ordinary skill in the art, and can be easily identified by a literature search as being described by Raben *et al.* (*J. Biol. Chem.* 273(30): 19086-19092 (1988); a copy of this reference is being filed concurrently in a Supplemental IDS). The Specification describes long-term experiments with this mouse model that were conducted, in which the animals were treated over time for periods up to 25 weeks, using different doses of enzyme (see p. 32, lines 21-30). The treated mice had decreased levels of glycogen in liver and perhaps in heart (see p. 32, lines 31-34); furthermore, in animals treated with high doses (2 mg/mouse, equivalent to 68 mg/kg as described at p. 32, lines 2-24), definite decreases in glycogen levels in liver, spleen, heart and skeletal muscle were found (p. 33, lines 5-8). Clear reversal of pathology has been demonstrated in various tissues, including heart and pectoralis muscle (see p. 35, lines 3-4). Thus, Applicants have clearly demonstrated a therapeutic effect in an appropriate mammalian model of the disease. The Specification

additionally describes pharmaceutical compositions incorporating acid alpha-glucosidase, as well as therapeutic methods (see, e.g., pp. 17 *et seq.*)

In support of the rejection, the Examiner indicated that de Barsy *et al.* (Birth Defects, Original Article Series, Vol. IX, No. 2, pp. 184-190 (1973)) and Williams *et al.* (Birth Defects, Original Article Series, Vol. XVI, No. 1, pp. 415-423 (1980)) disclose that although "one can measure a therapeutic effect manifested as an increase in enzyme activity in the tissues" after administration, the treatment regimens disclosed failed to alleviate outward symptoms of disease, and thus would indicate that undue experimentation would be necessary. However, neither de Barsy *et al.* nor Williams *et al.* describe continued administration of a therapeutically effective dose, such that the concentration of accumulated glycogen is reduced, and/or the accumulation of glycogen is arrested, as set forth in the amended claims. De Barsy *et al.* describe extraction of enzyme from human placenta and administration of a single dose to an infant. No morphologic improvement was noted after this single dose. Williams *et al.* describe administration of two doses of enzyme extracted from human liver and then linked to low density lipoprotein (LDL). Williams *et al.* concluded that their experiments were failures. For example, on page 420, they state:

> A quadriceps muscle biopsy was performed 2 days after the infusion and the glycogen content was not significantly altered. No α-glucosidase activity against glycogen was detected.

They also state that "The slight decrease in glycogen content of tissues is of questionable significance" (p. 422) and note that the patient died 26.5 days after the second infusion (p. 420).

In contrast to these two references, the present application has shown clear and significant reduction in glycogen content in a recognized mouse model for Pompe disease. In view of these considerations, as well as the detailed discussion in the Specification regarding methods of therapy, pharmaceutical preparations and representative infusion schedules, one of ordinary skill in the art would be able to practice the claimed methods without undue experimentation.

Rejection of Claim under 35 U.S.C. §102

The Examiner rejected Claim 1 under 35 U.S.C. §102(a), stating that it is anticipated by Kikuchi *et al.* (J. Clin. Invest. 101(4):827-833 (1998)). In order for a reference to anticipate claims, the reference must teach every aspect of the claimed invention either explicitly or impliedly (see M.P.E.P. 2131). Kikuchi *et al.* do not teach each aspect of the amended claim.

The claim, as amended, describes a method of treating a human patient with Pompe's disease, by intravenously administering biweekly to the patient a therapeutically effective amount of human acid alpha glucosidase, whereby the concentration of accumulated glycogen is reduced and/or further accumulation of glycogen is arrested. Kikuchi *et al.* describe administration of recombinant human acid alpha-glucosidase to acid maltase-deficient quail, and resultant increase in enzyme activity and decrease in glycogen levels in heart and liver, and essentially normal morphology in pectoralis muscle except for increased glycogen granules. Kikuchi *et al.* do not describe treatment of a human patient, and thus, do not teach this vital element of the claimed invention. In addition, the quail were injected seven times over a sixteen day period (p. 828, second column), and not biweekly. In view of these considerations, the claim is not anticipated by Kikuchi *et al.*

The Examiner also rejected Claim 1 under 35 U.S.C. §102(b) as being anticipated by de Barsy *et al.* or Williams *et al.* These two references have been discussed in detail above. As indicated, neither reference describes biweekly administration, nor do they describe administration of an amount of acid alpha-glucosidase in a therapeutically effective dose, such that the concentration of accumulated glycogen is reduced, and/or the accumulation of glycogen is arrested. In fact, de Barsy *et al.* indicate that "the amount of enzyme which [was] administered was very limited and obviously much to small to cause any major change" (p. 189, first full paragraph). Therefore, de Barsy *et al.* cannot teach a therapeutically effective dose.

In view of these considerations, the claimed invention is not anticipated by either de Barsy *et al.* or Williams *et al.*

The Examiner additionally rejected Claim 1 under 35 U.S.C. §102(e) as being anticipated by Reuser *et al.* (U.S. Patent 6,118,045). Reuser *et al.* teach transgenic nonhuman animals producing acid alpha glucosidase in milk. Reuser *et al.* do not describe treatment of a human patient, nor do they describe biweekly administration of a therapeutically effective dose to a human patient. In view of this consideration, the claim is not anticipated by Reuser *et al.*

Rejection of Claims under 35 U.S.C. §103

The Examiner rejected Claims 35-64 as being unpatentable over de Barsy *et al.*, Williams *et al.* and Reuser *et al.* in view of Bijvoet *et al.* (Biochim. Biophys. Acta 1308:93-96 (1996) and Van Hove *et al.* (Biochem. Mol. Biol. Int'l. 43(3):613-623 (1997)), stating that de Barsy *et al.*, Williams *et al.* and Reuser *et al.* demonstrates a therapeutic effect shown by an increase in enzyme activity in the tissues of infant patients, and that Bijvoet *et al.* and Van Hove *et al.* teach the obtaining of high amounts of enzyme.

As discussed above, neither de Barsy *et al.*, Williams *et al.* nor Reuser *et al.* describe biweekly intravenous administration to a human patient of an amount of acid alpha-glucosidase in a therapeutically effective dose, such that the concentration of accumulated glycogen is reduced, and/or the accumulation of glycogen is arrested. Neither Bijvoet *et al.* nor Van Hove *et al.* remedy the deficiencies of de Barsy *et al.*, Williams *et al.* and Reuser *et al.*

Bijvoet *et al.* describe transgenic production of acid alpha-glucosidase and its administration to cultured fibroblasts. They do not describe administration of an amount of acid alpha-glucosidase in a therapeutically effective dose to a human individual, such that the concentration of accumulated glycogen is reduced, and/or the accumulation of glycogen is arrested. Furthermore, Bijvoet *et al.* do not teach or suggest any particular dosage range for enzyme. Van Hove *et al.* describes preliminary attempts at production of recombinant acid alpha-glucosidase produced in Chinese hamster ovary (CHO) cells. As with Bijvoet *et al.*, they do not describe administration of an amount of acid alpha-glucosidase in a therapeutically effective dose to a human individual, such that the concentration of accumulated glycogen is reduced, and/or the accumulation of glycogen is arrested.

One of ordinary skill in the art, given the teachings of de Barsy *et al.*, Williams *et al.* and Reuser *et al.* in view of Bijvoet *et al.* and Van Hove *et al.*, would not have known whether administration of enzyme to human individuals would in fact have resulted in therapeutic efficacy.

To establish a reasonable expectation of success for obviousness, there must be "at least some degree of predictability" (see M.P.E.P. 2143.02). Predictability is determined at the time the invention was made: "whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made" (see *id.*). At the time Applicants' invention was made, Pompe's disease had been known for about seventy years, since the early 1930's, and the enzyme deficiency had been known for about forty years, since the 1960's. And yet, many attempts at treatment of the disease by administration of replacement enzyme had failed (see, e.g., Williams *et al.* and de Barsy *et al.*, discussed previously). In view of repeated failures known in the art, it is evident that at the time the invention was made, there was a long-felt need but no reasonable expectation of success.

In this context of the long-felt need for a treatment and the failure of others to treat Pompe's disease successfully, including attempts to treat the disease by enzyme replacement, one skilled in the art would not have had a reasonable expectation of success from the teachings of the references. Nevertheless, Applicants have in fact succeeded in treating patients with Pompe's disease, as evidenced by successful clinical trials that have led to the recent approval by the Food and Drug Administration of the product, Myozyme®, for the treatment of Pompe's disease. This incredible success in view of the long-felt need and failures of others makes the claimed invention non-obvious over the teachings of the cited references under 35 U.S.C. 103(a).

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry and consideration of the references cited in the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

David E. Brook, R.N. 22592

By for Elizabeth W. Mata

Elizabeth W. Mata
Registration No. 38,236
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
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